Optimizing the amount of dietary protein to maximally stimulate post-exercise muscle protein synthesis in elderly men.

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To define the amount of dietary protein required to optimally stimulate post-exercise muscle protein synthesis in the older population.To assess whether co-ingesting 1.5 g of free leucine (contained within 15 g dairy protein) along with 15 g protein...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Protein and amino acid metabolism disorders NEC
Study type	Interventional

Summary

ID

NL-OMON41601

Source
ToetsingOnline

Brief title
Active Aging Protein Dose Response

Condition

- Protein and amino acid metabolism disorders NEC
- Muscle disorders

Synonym
age-related muscle loss, Sarcopenia

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W,TIFN

Intervention

Keyword: Dietary Protein, Elderly, Exercise, Muscle Protein Synthesis

Outcome measures

Primary outcome

The main study endpoints are muscle protein synthesis (MPS) rates. In order to determine the MPS, the following parameters will be measured:

• Muscle protein-bound L-[ring-2H5]-phenylalanine enrichment (expressed as MPE)

• Muscle protein-bound L-[1-13C]-leucine enrichment (expressed as MPE)

• Plasma L-[ring-2H5]-phenylalanine, L-[1-13C]-KIC,enrichments (expressed as MPE)

Secondary outcome

Secondary endpoints include whole-body protein metabolism (synthesis, breakdown, oxidation, and net balance) and measures of digestion and absorption kinetics. Therefore, the following parameters will be measured:

• Plasma enrichments (in MPE) of:

o L-[ring-2H5]-phenylalanine

o L-[ring-2H4]-tyrosine

o L-[3,5-2H2]-tyrosine

• Plasma total phenylalanine and tyrosine concentrations (expressed as µmol/L)

• Total plasma amino acids (AAmax [µmol/L])

• Plasma glucose (glucosemax [mmol/L])

• Plasma insulin (insulinmax [mU/L])

Study description

Background summary

Aging is accompanied by a progressive decline in skeletal muscle mass. This age-related loss of muscle mass is attributed to an imbalance between rates of muscle protein synthesis and breakdown. As rates of basal muscle protein synthesis does not seem to differ between the young and elderly, most research has focused on potential impairments in the muscle protein synthetic response to the main anabolic stimuli, ie food intake and exercise. Skeletal muscle protein synthesis is highly responsive to food intake in healthy young adults. Recent data indicate that the muscle protein synthetic response to food intake may be blunted in the elderly. This proposed anabolic resistance is now being regarded as a key factor in the etiology of sarcopenia. Effective strategies to prevent and/or counteract the age related loss of muscle mass include protein supplementation, preferably in combination with resistance type exercise training. Recent studies show the efficacy of dietary protein supplementation to improve muscle strength and function in frail elderly (14) and to further augment the gains in muscle mass and function when combined with resistance type exercise training (13). As combining proper nutrition with exercise has numerous synergistic benefits, nutrition research is warranted to define the optimal amount, type and timing of protein that needs to be consumed to maximize post-exercise muscle protein synthesis rates in the older population.

Improvements in protein balance and/or higher muscle protein synthesis rates have been reported following the ingestion of various types of dietary protein: whey protein (2), casein protein (2), soy protein (15), casein protein hydrolysate (8, 9), egg protein (10), and wholemilk and/or fat-free milk (5, 15). It seems obvious to question which source of dietary protein is most effective to promote muscle protein synthesis. There is only limited research comparing the efficacy of the ingestion of different proteins sources on the post-exercise muscle protein synthetic response. As such, it is difficult to identify a specific protein source that is most potentiating. The amount and timing of protein administration, the leucine content of the protein, and the digestion and absorption kinetics of the protein source may all modulate the post-exercise muscle protein synthetic response. Milk protein and its main isolated constituents, whey and casein, are the most widely studied dietary proteins. Casein and whey protein seem to have distinct anabolic properties, which are attributed to differences in digestion and absorption kinetics (1-4). Whereas whey protein is a soluble protein that leads to rapid intestinal absorption, intact casein clots in the stomach delaying its digestion and absorption and the subsequent release of amino acids in the circulation (7). The fast, but transient rise in plasma amino acid concentration after whey protein ingestion can lead to higher protein synthesis and oxidation rates (1, 3, 4). In addition to intrinsic differences in digestion and absorption rate, it has been suggested that whey protein can more effectively stimulate

(post-exercise) protein synthesis due to its greater leucine content when compared to casein (11, 12).

In young men it was reported that ingestion of 20 g intact whole egg protein is sufficient to maximally stimulate MPS after resistance exercise (Moore, 2009). In older men it was found that the optimal whey protein dose for non-frail older adults is 20 g in order to increase myofibrillar MPS above fasting rates. However, resistance exercise increased MPS in the elderly to the greatest extent with 40 g of whey ingestion (Yang 2012). Another study (Robinson, 2009) on unilateral resistance exercise in middle-aged men found that ingestion of 170 g of beef protein (36 g protein) is required to stimulate a rise in myofibrillar MPS above that seen with lower doses. Since ~40g of protein was the maximal dose in these studies and no plateauing effect occurred, it is scientifically relevant to test 60 g protein and identify the upper limit to post-exercise dietary protein ingestion. In addition, these studies lack data on whole body protein kinetics, which explains how excess protein is utilized even when muscle sensitivity towards additional protein is no longer being achieved. Lastly, the efficacy of co-ingesting leucine along with dairy protein after whole-body resistance exercise has never been investigated.

Study objective

To define the amount of dietary protein required to optimally stimulate post-exercise muscle protein synthesis in the older population.

To assess whether co-ingesting 1.5 g of free leucine (contained within 15 g dairy protein) along with 15 g protein can achieve a maximal muscle protein synthetic response as opposed to simply increasing the amount of protein consumed.

Study design

Screening Trial:
When volunteers respond to the advertisement, we contact them by e-mail/phone and briefly explain the study. We will provide them with the information brochure and the informed consent (which they will bring during the screening). To assess whether volunteers are eligible to participate in this study, we will invite them to the University for a screening. They will be screened in a fasting and rested state, meaning that they are not allowed to eat and drink (except for water) from 22h00 the night prior to the screening, and that they have to come to the University by car or public transport. Before we start the screening, we will explain the entire experimental trial and answer any potential questions. We will then ask them to read, fill out, and sign the informed consent form. After signing the informed consent form, we will start the screening by going through the medical questionnaire to assess their general health, use of medication, and physical activity. Subsequently, we

place a catheter into the antecubital vein for blood collection. After the first (basal) blood draw, subjects receive a drink containing 82.5 g of dextrose monohydrate, and blood glucose will be measured every 30 minutes for 2 hours (2 h oral glucose tolerance test, OGTT). The glucose drinks will be prepared in the dietary kitchen of the department of human biology. In the basal blood sample we will also determine HbA1c as a marker of long-term hyperglycemia. When subjects appear to be glucose intolerant based on these measurements according to the WHO (16), they cannot participate in this study. Furthermore, blood pressure will be measured. Subjects with hypertension (>140/90 mmHg) will also be excluded from participation. After completion of the 2 h OGTT and providing the subject with a sandwich, we will assess body composition by performing a dual-energy X-ray absorptiometry (DEXA) scan and measure body height, body weight, and leg volume. DEXA is a simple and non-invasive procedure, which will take place at the University. Subjects will be instructed to lie down on a table and stay motionless for approximately 3 minutes during which the body scan takes place. Performing the above mentioned tests allow us to characterize the participants. In case of an unexpected medical finding, it is our duty to inform the subjects. If a participant does not want to receive this information, he cannot participate in this study. During the screening visit, subjects will be asked to fill in an exercise questionnaire to gather information on past and present exercise habits

On a separate day, successfully screened subjects will return to the university to be familiarized and tested for strength on the exercise machines. However, prior to any physical exertion, all subjects will have an electrocardiogram (ECG) measured at rest and during a submaximal workload on an exercise bike, consisting of 10 min cycling at 70% of estimated heart rate max (220 - age x 0.70). A cardiologist at the University Hospital will analyze all ECG data and determine if the subject can safely tolerate further exercise testing. Following approval by the cardiologist, subjects will then be instructed on proper weight-lifting technique on each exercise machine (chest press, lat pulldown, leg-press and leg-extension) and complete a standardized testing protocol to determine a measurement of maximal strength (1RM) on each exercise machine. The testing protocol requires that the subjects complete sets on each exercise machine increasing in weight until volitional fatigue occurs, ideally occurring between 3-6 repetitions on the heaviest weight. The attained strength data will be compared to previously published data and used to calculate an estimation of 1RM

Experimental Trial:

After the subjects arrive at the University, we will check if they met all the requirements described in section 3.2, ask them to put on their shorts, and assign them to a bed. A catheter will be inserted into the antecubital vein for basal blood collection (10 mL, t=-120) and subsequent stable isotope amino acid tracer infusion. A second catheter will be inserted into antecubital vein of the contralateral arm for blood collection. After a pre-infusion period of 60

minutes (t=-60), the participant will begin to complete the exercise regimen, which will last 60 minutes. The exercise bout will consist of a 5-minute warm-up on a cycle ergometer, followed by 2 sets of chest press and lat pulldown, and 5 sets of leg-press and 4 sets of leg-extension. For each of the upper body exercises, the workload will be set at 80% of 1-RM (10 repetitions per set). For each of the lower body exercises, the workload of the first set will be set at 50% (10 repetitions), then increased to 70% (10 repetitions per set) for the remaining 4 sets. Resting periods of 2 minutes will be allowed between all sets and exercises. After completing the exercise, participants will have a muscle biopsy taken (t=0) from the vastus lateralis muscle of a randomized leg. The participant will then ingest a randomized dose of dairy protein in the amount of 0, 15, 30, 45 g or 15 g + 1.5 g free leucine dissolved in 500mL of vanilla-flavoured water. Following the ingestion of the protein dose another muscle biopsie, at 6 hours (t=360) will be sampled from the vastus lateralis of a randomized leg.
The timing of the post-exercise muscle biopsies is intended to most accurately determine aggregate (0h - 6h) rates of muscle protein synthesis (MPS). It is generally assumed that peak MPS rates are more meaningful in predicting long-term phenotypic outcomes (muscle hypertrophy) than MPS calculated over a longer period. However, taking a muscle biopsy at t=300 allows for the determination of the stimulatory effect of each separate protein dose during the respective digestion periods, which is physiologically relevant information with regard to the anabolic response to feeding. Muscle biopsies will be taken through separate incisions divided over the two legs to reduce discomfort. A total of 12 blood samples (10 mL) will be collected throughout the experimental trial. A background blood sample will be collected immediately prior to the start of the tracer infusion along with 2 samples at 2 and 1 hour before the drink. Sampling frequency will increase to every 15min directly after the ingestion of the drink for a period of one hour. After the first hour, blood sampling will occur every half hour for the remaining 3 hours (t=60-300)

Intervention

The exercise bout will consist of a 5-minute warm-up on a cycle ergometer, followed by 2 sets of chest press and lat pulldown, and 5 sets of leg-press and 4 sets of leg-extension. For each of the upper body exercises, the workload will be set at 80% of 1-RM (10 repetitions per set). For the leg press, the workload of the first set will be set at 50% (10 repetitions), then increased to 70% (10 repetitions per set) for the remaining 4 sets. For the leg extension, all 4 sets are done at 80% 1RM. Resting periods of 2 minutes will be allowed between all sets and exercises. After completing the exercise, participants will have a muscle biopsy taken and will then ingest a randomized dose of dairy protein in the amount of 0, 15, 30, 45 g or 15 g + 1.5 g free leucine dissolved in 500mL of vanilla-flavoured water.

Study burden and risks

The burden and risks associated with participation are small. Insertion of the catheters is comparable to a blood draw and could result in a small hematoma. Muscle biopsies will be taken under local anesthesia by an experienced physician, but may cause some minor discomfort for maximally up to 24 h after completion. The discomfort is comparable to muscle soreness or the pain one has after bumping into a table. We will take 5 (6mL) and 12 blood samples (10 mL) during the screening and experimental trial respectively. The total amount of blood we draw is less than half the amount of a blood donation and will be completely restored in approximately 1 month. For both the screening and the experimental trial, participants have to be fasted, so they are not allowed to eat and drink (except for water) from 22h00 the evening before. Also, 2 days prior to the experimental trial participants should keep their diet as constant as possible, do not perform any type of intense physical exercise, and do not consume alcohol. Furthermore, we will ask the participants to fill out a dietary record for 2 days prior to the experimental trial.
The types of protein used in the beverages are commercially available food products. Therefore, the test beverage does not form any health risks. The stable isotope amino acids tracers applied in this experiment are not radioactive and are completely safe. The production of the tracers for intravenous administration will occur in a sterile environment according to GMP guidelines.
There is no risk associated with the DEXA scan. The radiation dose emitted during a DEXA scan is 0.001 mSv. This is a very low exposure compared to the total background radiation in the Netherlands, which is ~2.5 mSv/year. For comparison, the radiation dose during a flight higher than 10 km is 0.005 mSV•h-1.
There is no direct benefit for the participants, only their contribution to scientific knowledge and nutritional strategies that prevent muscle loss in the elderly, which will be obtained from this study and can be used in the future.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy males
Age between 55 and 80 y
BMI between 18.5 and 30 kg/m2

Exclusion criteria

Celiac disease
Lactose intolerance
Smoking
Diabetes
Diagnosed GI tract diseases
Arthritic conditions
A history of neuromuscular problems
Any medications known to affect protein metabolism (i.e. corticosteroids, non-steroidal anti-inflammatories, or prescription strength acne medications).
Participation in exercise program
Hypertension, high blood pressure that is above 140/90 mmHg.
Cancer
Cardiovascular diseases
Donated blood within the last 3 months

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-07-2014
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	02-06-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 25434
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL47671.068.14
OMON	NL-OMON25434